SYNTHESIS OF QUATERNARY AMMONIUM DERIVATIVES OF BIOLOGICALLY ACTIVE HEXITOLS

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Alditols and anhydroalditols are widespread in both the animal and plant kingdoms. They are used in pharmaceutics, as sweeteners, inhibitors and in organic synthesis. Levels of 1,5-anhydro-D-glucitol in human blood are the first symptoms of many diseases e.g. type 2 diabetes or cardiovascular disease. Currently chemists and biologists are concentrated in synthesizing nucleoside mimetic's where sugar moiety is substituted with anhydroalditol e.g. 1,4-anhydro or 1,5-anhydro. There are information about inhibitory properties of alditol derivatives against HIV-1 retrovirus proteases [1].

Quaternary ammonium salts (QAS), a group of cationic surfactants which are used in many fields of everyday life such as: pharmaceutics, disinfectants, corrosion inhibitors, fungicides or pesticides. They exhibit antibacterial and antifungal activity, employed in many antimicrobial drugs. Typical QAS contains hydrophilic, cationic head and hydrophobic alkyl chain. Amfifilic character allows these compounds to bind to the cell membranes. For model quaternary ammonium salts optimal activity was achieved when alkyl chain is between 10 and 14 carbon atoms long [2].

Actually we are working on the synthesis: *N*-(1,5-anhydro-6-deoxy-hexitol-6-yl)aminium tosylates with configuration of alditol moiety: D-galakto, D-gluko and D-manno. First stage of synthesis was cyclization of hexitols in 5% solution of sulfuric acid. After purification primary hydroxyl groups of 1,5-anhydro derivatives were protected with trityl group. Reaction of 1,5-anhydro-6-trityl-hexitols with benzoyl chloride gave per-*O*-benzoylated derivatives (**3**). Deprotection of primary hydroxyl group and then reaction with tosyl chloride in pyridine gave expected products (**5a**, **5b**, **5c**) with good yields.
Quaternization of compounds **5a** and **5b** using pyridine and trimethylamine in ethanol gave expected products. Synthesis of: **6cP** and **6cT** was unsuccessful in any tested conditions. This could be explained by steric effect, the reaction center is blocked by bulky benzoyl protecting group at C4 carbon atom.
Due to difficulties with purification compounds **6aP**, **6aT**, **6bP** and **6bT** were directly treated with methanolic solution of sodium methoxide, pure products **7aP**, **7aT**, **7bP** and **7bT** were obtained with good yields.
All synthesis steps are presented on **Scheme 1**.

The structures of products were determined by spectral analysis including ^{1}H NMR ^{13}C NMR and extensive 2D NMR. **Table 1** and **2** presents analyses of NMR spectra for synthesized ammonium salts (**7aP**, **7aT**, **7bP** and **7bT**). **Figure 1** presents ^{1}H NMR spectra of compound **7bP**.

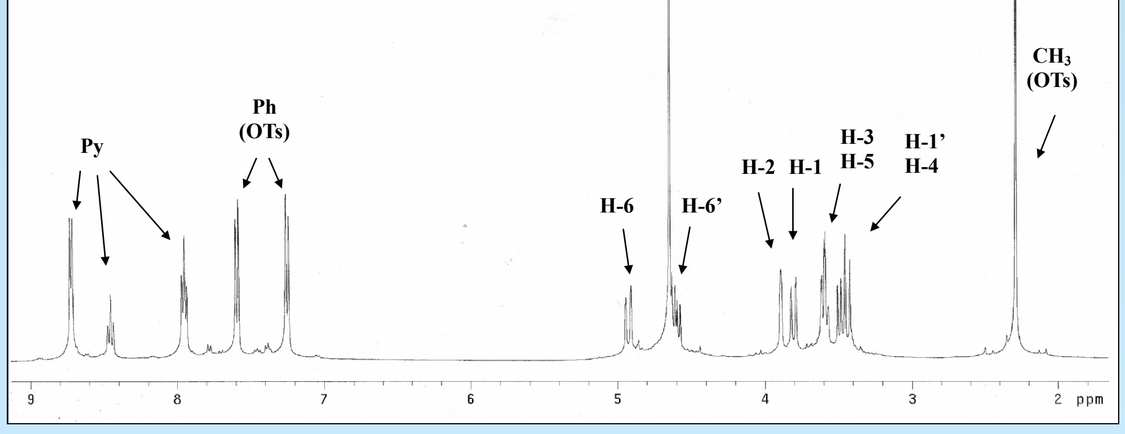
Table 1. Chemical shifts (ppm) in the ^{1}H NMR spectra for ammonium salts in D_2O solution.

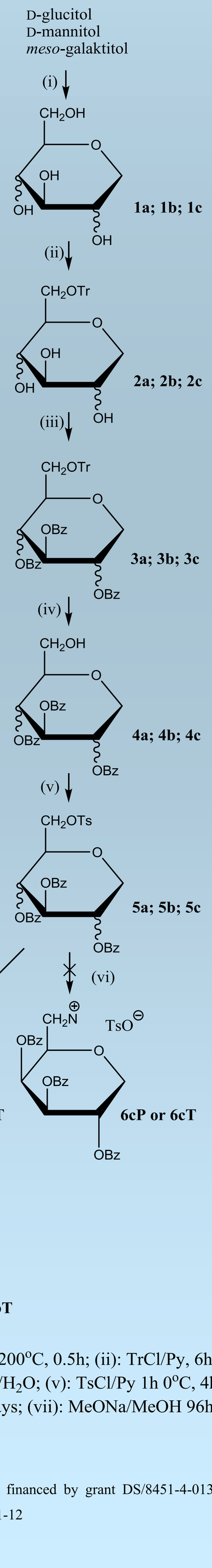
	H-1	H-1'	H-2	H-3	H-4	H-5	H-6	H-6'	cation	anion
7aP	3.82; **dd**, 1H	3.04; **t**, 1H	3.45; **m**, 1H	3.36; **t**, 1H	3.14; **t**, 1H	3.62; **m**, 1H	4.87; **dd**, 1H	4.56; **dd**, 1H	8.68-7.91; **m**, 5H	2.28; **s**, 3H (MePh) 7.59-7.25; **2d**, 4H (Ph)
7aT	3.84; **dd**, 1H	3.65-3.57; **m**, 1H	3.92; **m**, 1H	3.68; **t**, 1H	3.47-3.38; **m**, 1H	3.65-3.57; **m**, 1H	3.65-3.57; **m**, 1H	3.47-3.38; **m**, 1H	3.10; **s**, 9H	2.31; **s**, 3H (MePh) 7.63-7.28; **2d**, 4H (Ph)
7bP	3.80; **dd**, 1H	3.45; **t**, 1H	3.89; **d**, 1H	3.59; **m**, 1H	3.48; **t**, 1H	3.59; **m**, 1H	4.92; **dd**, 1H	4.60; **dd**, 1H	8.73-7.93; **m**, 5H	2.28; **s**, 3H (MePh) 7.60-7.24; **2d**, 4H (Ph)
7bT	3.95; **dd**, 1H	3.26; **t**, 1H	3.63-3.49; **m**, 1H	3.16; **m**, 1H	3.74; **t**, 1H	3.45-3.37; **m**, 1H	3.63-3.49; **m**, 1H	3.45-3.37; **m**, 1H	3.10; **s**, 9H	2.32; **s**, 3H (MePh) 7.64-7.28; **2d**, 4H (Ph)

Table 2. Chemical shifts (ppm) in the ^{13}C NMR spectra for ammonium salts in D_2O solution.

	C-1	C-2	C-3	C-4	C-5	C-6	cation	anion
7aP	68.97	69.33	77.46	70.99	78.06	62.37	146.39 145.26 128.17	142.63 139.75 129.65 125.58 20.68
7aT	69.80	68.88	74.77	67.50	73.45	68.15	54.35	142.69 139.75 129.68 125.61 20.69
7bP	70.30	69.05	78.38 or 73.49	68.43	78.38 or 73.49	62.46	146.33 145.26 128.20	142.59 139.83 129.66 125.60 20.70
7bT	68.74	69.15	71.00	74.71	77.52	67.54	54.35	142.69 139.77 129.69 125.61 20.70

Figure 1. ^{1}H NMR spectra of 7bP in D_2O solution.





Scheme 1: Reagents and conditions; (i): 5% H_2SO_4, 200°C, 0.5h; (ii): TrCl/Py, 6h, 60°C; (iii): BzCl/Py 1h 0°C, 3h RT; (iv): CH_3COOH/H_2O; (v): TsCl/Py 1h 0°C, 4h RT; (vi): Py 70°C 14 days or $N(CH_3)_3$ in EtOH 70°C 7 days; (vii): MeONa/MeOH 96h RT

References:

[1] V. Glacon, M. Benazza, A. El Anzi, D. Beaupere *J. Carbohydr. Chem.* 23, 95-110, 2004

[2] T. Abel, JL. I. Cohen, R. Engel, M. Filshtinskaya, A. Melkonian, K. Melkonian *Carbohydr. Res.* 337, 2495-2499, 2002

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